REMARKS

Formal Matters

Claims 1-45 and 48-50 remain in this application. Claims 46-47 were previously canceled. Claims 18, 19, 21 have been withdrawn as the result of being drawn to a non-elected species, while claims 28-45 and 48-50 have been withdrawn as a result of an earlier restriction. No claim is amended or added.

In view of the Examiner's earlier restriction requirement, applicants retain the right to present the subject matter of the withdrawn claims in a divisional application.

In his response dated August 8, 2005, the Examiner has indicated that he did not consider all of Applicants' arguments to the obviousness rejection under 35 U.S.C. § 103(a) in light of the fact that the Examiner did not receive all of the references submitted on the Supplemental Information Disclosure Statement, Form 1449.

Applicants respectfully submit that the missing references were due to patent office and not Applicants' error. Inclusion of the missing references is corroborated by Applicants' post card which indicates that all of the non-U.S. patent references (*i.e.*, 3 of 4 total) on the Form 1449 were indeed initially submitted on June 23, 2005.

In light of this, Applicants hereby are transmitting a duplicate copy of the Supplemental Information Disclosure Statement along with duplicate copes of the references in question. Applicants respectfully request reconsideration of all of the arguments along with the corroborating documentation previously submitted on June 23, 2005. For the Examiner's convenience, Applicants have reproduced the previous argument below.

Applicants further request the Examiner telephone the undersigned if the references in question still appear to be missing from the packages of information presented to the Examiner.

Rejection Under 35 U.S.C. § 103(a) over Andya et al. (WO 97/04801) in view of Relton et al., (WO 97/45140), Kaisheva et al., (US2003/0113316) and Merck Index (Merck Index, 10th Ed., 1983, p.797-798).

Claims 1-17, 20 and 22-27 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Andya in view of Relton et al., Kaisheva et al. and Merck Index.

The Examiner alleges that Andya discloses antibody formulations having an osmotic pressure of 250-350 Osm, antibody concentrations ranging from at least 80 mg/ml to 300 mg/ml, lyoprotectants (e.g., trehalose) ranging from 30 mM to 300 mM and various administration methods including injection devices, including syringes and auto-injectors.

The Examiner further alleges that Relton et al., teaches antibody formulations having a kinematic viscosity ranging from 1-9 cP, while Kaisheva et al. discloses the use of arginine and trehalose, among other adjuvants, as cryoprotectants.

The Examiner further alleges that as arginine is strongly alkaline, in order to maintain the pH 5.5-7 of the Andya *et al.* formulation, addition of acid or association with HCl would be required.

In response, Applicants respectfully submit that the combined teaching do not suggest the selection of arginine-HCL as being particularly suited for formulating antibodies at high concentrations. None of the above references teach the delicate balance between viscosity, stability, osmolarity and turbidity. That is, while increasing concentrations of charged excipients may decrease viscosity, doing so also increases the concentration of solutes in the solution, which in turn increases osmolarity. As applicants note in Figure 6, not all excipients have the same effect on viscosity and turbidity, and it is the selection of the particular combination of excipients arginine-HCl, histidine and polysorbate of claim 1 that achieves the delicate balance of low turbidity, physiological osmolarity and low viscosity, while preserving protein stability.

The fundamental issue here is the creation of a pharmaceutical formulation. At higher concentrations of antibody, the problems to resolve in creating an acceptable formulation are multiplied. At lower concentrations, the primary concern is antibody stability, or ensuring that

sufficient excipients are available to ensure proper protein folding and stability. A lyophilized formulation further requires "cryoprotectants" or agents that are present to minimize the stresses created by the freezing, thawing and lyophilization process. As applicants have discovered, as protein concentration increases, it is not a simple matter of just adding more excipients. Some excipients increase viscosity in and of themselves (*e.g.*, sucrose, trehalose), while others do not decrease the viscosity resulting from the increased protein concentration. Moreover, higher and higher levels of excipients create osmotic pressure, thus creating an upper limit of all dissolved solids in order to avoid having extreme hyper-osmotic solutions. As a result, as the protein concentration is increased, it becomes more and more important to select excipients that serve multiple roles - stabilizers, buffers, tonicity modifiers, viscosity adjustment, *etc.* It is precisely the realization of the multiple role that arginine-HCl plays that makes it such an effective agent in high concentration protein formulations.

Kaisheva is defective as a reference for the Examiner's argument because it does not recognize the problem of increased turbidity that can result when certain excipients are added at higher concentrations.

The protein concentrations recited in Kaisheva are "greater than 50 mg/ml" while those of the present invention are significantly higher at "100 - 260 mg/ml". While the paper description of the antibody concentration of the Kaisheva formulation implies an overlap with Applicants' formulation, the highest concentration that Kaisheva actually produced with their formulation was only 50 mg/ml. Because osmolarity is a measure of the total dissolved solids, it represents a real limit to the amount of excipients that can be present. This absolute excipient limit is not recognized by Kaisheva. In fact, the long list of "cryoprotectants" suggested by Kaisheva in paragraph 29 (in which arginine appears) implies that the recited examples of polymers, sugars, surfactants and amino acids are interchangeable - when in fact, only the selection of two of these, in *combination,* not individually, *i.e.*, polysorbate and arginine, will solve Applicants' problem.

Moreover, as reported in Carpenter *et al.*, *Pharmaceutical Res.* 14:8: 969 (1997), the use of reducing sugars, which can react with and degrade the protein with which they are formulated, should be avoided. Surprisingly, two of the sugar excipients suggested by Kaisheva as acceptable excipients are the reducing sugars glucose and lactose (p.972). Continuing, Carpenter also cautions against the use of "crystalline excipients" such as mannitol and glycine. Unless formulated in a precise and acceptable ratio, these agents do not provide sufficient stabilization during the lyophilization process (p. 970 and 973). While Kaisheva does not suggest the use of mannitol, the point here is that glycine is not an acceptable excipient unless it is formulated in a precise molar ratio with mannitol, an important point which Kaisheva does not realize even at relatively low antibody concentrations.

In summary, the actual experimental concentration of the Kaisheva formulations does not approximate Applicants, all of the Kaisheva excipients are not interchangeable in Applicants formulation, and the particular problems presented by each are distinct. As a result, Applicants respectfully submit that the disclosure of Kaisheva either alone or combination with the other cited reference, does not render obvious Applicants' claimed invention.

The deficiencies of Kaisheva are not remedied by the remaining references. None of the cited references even recognize how viscosity can be lowered and still maintain the claimed limitations of osmolarity and turbidity. Andya does not recognize the problem of higher viscosities at high antibody concentrations, while Relton does not address how the viscosity of high concentration antibody formulations may be reduced. Merck is not even directed to antibody formulations.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-17, 20 and 22-27 under 35 U.S.C. § 103(a).

SUMMARY

Claims 1-45 and 48-50 are pending in the application. No claim is canceled or amended herein.

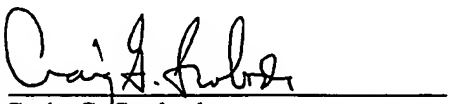
If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and no fees are believed due for timely consideration. In the unlikely event that fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: **November 7, 2005**

By: 

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